End Glycated Proteins In Pregnant Diabetics With Pregnancy Induced Hypertension

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ACE	Angiotensin-converting enzyme
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ADHD	Attention-deficit/hyperactivity disorder
AEDFV	Absent end-diastolic flow velocity
ALT	Alanine Amino-Transferase
ARBs	Angiotensin II receptor blockers
AST	Aspartate Amino-transferase
BMI	Body Mass Index
ChIPs	Chromatin immunoprecipitations
CRP	C-reactive protein
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
GDM	Gestational Diabetes mellitus
GH	Gestational hypertension
H3K9	Histone methylated on K9
HbA_{1C}	Glycated Hemoglobin
HLA	Human leucocytic antigen
HUVEC	Human umbilical vein endothelial cells
IADPSG	International Association of Diabetes and Pregnancy Study Group
IGF	Insulin like growth factor
iNOs	Isoenzyme Nitric oxide synthases

IOM	Institute of Medicine
IRs	Insulin receptors
IUGR	Intra uterine growth retardation
LGA	Large for gestational age
MCP-1	Monocyte chemotactic protein-1
NO	Nitric oxide
NPH	Neutral protamine hagedorn
NST	Nonstress test
OGTT	Oral Glucose tolerance test
PG	Prostaglandins
PI	Pulsatility index
PIH	Pregnancy Induced Hypertension
RDS	Respiratory distress syndrome
RI	Resistance index
S/D	Systolic/ Diastolic
SBP	Systolic blood pressure
SC	Subcutaneously
SD	Standard Deviation
SGA	Small for gestational age
SMC	Smooth muscle cells
SOGC	Society of Obstetricians and Gynecologists of Canada
STZ	Streptozotocin
USPSTF	United States Preventive Services Task Force
VCAM-1	Vascular cell adhesion molecule-1
VE	Vascular endothelium
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

INTRODUCTION

Introduction and Aim of The Work

Introduction

Diabetes mellitus is described as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action or both ***(Alberti and Zimmet, 1998).***

Physiological insulin resistance is noted during late pregnancy and patients with gestational diabetes show more insulin resistance compared with pregnant control subjects with normal glucose tolerance ***(Witlin AG and Sibai BM, 1999).***

Pregnancy induced hypertension (PIH) and /or pre-eclampsia have been associated with hyperinsulinemia in both cross-sectional study designs ***(Kaaja R et.al., 1995)*** and cohort studies ***(Sowers JR et.al., 1995).***

Glycosylated hemoglobin (HbA_{1C}) level reflects the average plasma glucose to which the hemoglobin is exposed during the erythrocyte's life span of about 90 days and may be less influenced by the acute stress of illness ***(Laura SG et.al., 2003).***

Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes. Several studies have established an association between elevated maternal glucose or glycated hemoglobin levels during embryogenesis and

high rates of spontaneous abortions and major malformations in newborns ***(Kitzmiller JL et.al., 1996).***

Ducey et.al., 1987, stated that a description of uterine systolic/diastolic (S/D) ratio should be part of the clinical evaluation of all pregnant women with hypertension ***(Chein et.al., 2000).***

Aim of the work

The aim of this work is to study the levels of end glycated proteins in pregnant diabetics with PIH and the relation of levels of HbA_{1C} to the fetal and placental blood flow in these patients.

REVIEW

Chapter 1

Pregnancy and Diabetes Mellitus

Normal pregnancy has been characterized as a "diabetogenic state". Abnormal maternal glucose regulation occurs in 3-10% of pregnancies. Pregnancy is characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia, thus it may predispose some women to develop diabetes.

Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Insulin sensitivity is reduced by as much as 80%. Placental secretion of hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone, is a major contributor to the insulin-resistant state seen in pregnancy. The insulin resistance likely plays a role in ensuring that the fetus has an adequate supply of glucose by changing the maternal energy metabolism from carbohydrates to lipids. There is increased maternal adipose deposition, decreased exercise, and increased caloric intake. These and other endocrinologic and metabolic changes ensure that the fetus has adequate supply of fuel and nutrients at all times. Gestational diabetes occurs when pancreatic function is not sufficient to overcome the insulin resistance created by changes in diabetogenic hormones during pregnancy ***(Cianni et al., 2003)***.

On the other hand, the adipose tissue is now considered an active organ, capable of secreting substances such as adipokines, which may play a role in the pathogenesis of insulin resistance. Resistin, leptin serum and placental levels increase as pregnancy progresses, which is in contrast to

levels of adiponectin. These levels correlate with the state of reduced insulin sensitivity often developed in the latter stages of pregnancy ***(Gomez et al, 2008)***

Maternal-Fetal Metabolism in Diabetes mellitus:

If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results. This typically manifests as recurrent postprandial hyperglycemic episodes. These postprandial episodes are the most significant source of the accelerated growth exhibited by the fetus.

Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia. Fetal hyperinsulinemia promotes excess nutrient storage, resulting in macrosomia. The energy expenditure associated with the conversion of excess glucose into fat causes depletion in fetal oxygen levels.

These episodes of fetal hypoxia are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red cell hyperplasia, and increased hematocrit. Polycythemia (hematocrit >65%) occurs in 5-10% of newborns of diabetic mothers. This finding appears to be related to the level of glycemic control and is mediated by decreased fetal oxygen tension. High hematocrit values in the neonate lead to vascular sludging, poor circulation, and postnatal hyperbilirubinemia.

During a healthy pregnancy, mean fasting blood sugar levels decline progressively to a remarkably low value of 74 ± 2.7 (standard deviations [SD]) mg/dL. However, peak postprandial blood sugar values rarely exceed 120 mg/dL. Meticulous replication of the normal glycemic profile

during pregnancy has been demonstrated to reduce the macrosomia rate. Specifically, when 2-hour postprandial glucose levels are maintained below 120 mg/dL, approximately 20% of fetuses demonstrate macrosomia. If postprandial levels range up to 160 mg/dL, macrosomia rates rise to 35%.

New terminology and diagnostic criteria:

The term "gestational diabetes" has been used to define women with onset or first recognition of abnormal glucose tolerance during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) continues to use this terminology ***(Committee opinion no. 504, 2011)***.

However, in 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, recommended a change to this terminology ***(International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger et al., 2010)***. In this system, diabetes diagnosed during pregnancy is classified as overt or gestational. In January 2011, the American Diabetes Association (ADA) endorsed this recommendation. ***(American Diabetes Association, 2011)***

Overt diabetes:

A diagnosis of overt diabetes can be made in women who meet any of the following criteria at their initial prenatal visit:

- Fasting plasma glucose ≥126 mg/dL, or
- HbA_{1C} ≥6.5 percent using a standardized assay, or
- Random plasma glucose ≥200 mg/dL that is subsequently confirmed by elevated fasting plasma glucose or HbA_{1C}.

These thresholds were chosen because they correlate with development of adverse vascular events, such as retinopathy and coronary artery disease.

The rationale for this change is that an increasing proportion of young women have overt but as yet unrecognized type 2 diabetes due to the increasing prevalence of obesity and lack of routine glucose screening/testing in this age group.

In addition, about 10 percent of women formerly classified as having gestational diabetes have circulating islet-cell antibodies; these women may have a "latent" form of type 1 diabetes ***(Järvelä et al., 2006)***. Their risk of developing type 1 diabetes is not known, but specific Human leucocytic antigen (HLA) alleles (DR3 or DR4) appear to predispose to the development of type 1 diabetes after delivery, as does the presence of islet-cell antibodies ***(Ferber et al., 1999)***. Gestational diabetes in lean pregnant women, need for insulin treatment of gestational diabetes, diabetic ketoacidosis during pregnancy, and postpartum hyperglycemia also suggest preexisting unrecognized type 1 diabetes.

Identifying overt diabetes early in pregnancy may be important because these women are at increased risk of having a child with a congenital anomaly and may be at increased risk of complications from diabetes (nephropathy, retinopathy) ***(Omori and Jovanovic, 2005)***. Early identification and treatment of hyperglycemia may reduce these risks.